<table>
<tr><th>Claim Element</th><th>Glaxo's Position</th><th>Teva's Position</th></tr>
<tr>
<td></td>
<td>evidence quoted and cited in the discussion of claim 1 above. In addition, Glaxo wishes to call the Court's attention to the following intrinsic evidence specifically related to claim 2.<br><br>'249 patent, Col. 1:54-56 (Ex. 1):<br><br>"The amount of ethanol present in the formulation is such that the resulting formulation has the enhanced stability. Preferably the amount of ethanol in the composition on a weight/volume basis of the complete formulation, is within the range 2.5% to 10%, and more particularly is between 5 to 10% w/v, more especially 7-8% w/v." (Emphasis added).<br><br>'249 patent, Col. 2:30-34 (Ex. 1):<br><br>"The amount of ethanol in the formulation for oral administration, expressed as a percentage of the complete formulation on a weight/volume basis, is preferably within the range 2.5 to 10%, and more particularly between 5 to 10%, more especially 7-8%." (Emphasis added).</td>
<td>containing 7% to 8% weight/volume ethanol based on the complete formulation.<br><br>'249 patent, claim 12 (Ex. 1):<br><br>12. A pharmaceutical composition according to claim 11 wherein said pH is obtained by the use of buffer salts.<br><br>'249 patent, Col. 2:30-34 (Ex. 1):<br><br>"The amount of ethanol in the formulation for oral administration, expressed as a percentage of the complete formulation on a weight/volume basis, is preferably within the range 2.5 to 10%, and more particularly between 5 to 10%, more especially 7-8%."<br><br>'249 patent, Col. 2:53-65 (Ex. 1):<br><br>"Ranitidine oral liquid formulation (150 mg/10ml) expressed as free base<br>
<table>
<tr><th></th><th>% w/v</th></tr>
<tr><td>Ranitidine hydrochloride</td><td>1.68</td></tr>
<tr><td>Ethanol</td><td>7.5</td></tr>
<tr><td>Potassium dihydrogen orthophosphate</td><td>0.095</td></tr>
<tr><td>Disodium hydrogen orthophosphate anhydrous</td><td>0.350</td></tr>
<tr><td>Hydroxypropylmethylcellulose</td><td>qs</td></tr>
</table>
</td>
</tr>
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|---|---|---|
| | **'249 patent, Col. 2:47-65 (Ex. 1):**<br><br>"An illustrative example of a formulation according to the invention is as follows. . . .<br><br>Ranitidine oral liquid formulation (150 mg/10 ml) expressed as free base<br><br>% w/v<br>Ranitidine hydrochloride 1.68<br>*Ethanol* *7.5*<br>Potassium dihydrogen orthophosphate 0.095<br>Disodium hydrogen orthophosphate anhydrous 0.350<br>Hydroxypropylmethylcellulose qs<br>Preservative qs<br>Sweetening agents qs<br>Flavour qs<br>Purified water BP to 100ml. "<br>(Emphasis added).<br><br>**'249 prosecution history, Request for Reconsideration dated May 10, 1991 (Ex. 3, G000202-11):**<br><br>"Applicant submits herewith a Declaration of Dr. John Hempenstall which provides convincing evidence that the compositions of the present invention show a quite unexpected advantage over the teachings of GB-A-2142820 *in terms of the stability of the ranitidine in the composition*. In this connection, it is noted that the liquid formulation | Preservative qs<br>Sweetening agents qs<br>Flavour qs<br>Purified water BP to 100ml." |

| Claim Element | Glaxo's Position | Teva's Position |
|---|---|---|
| | without ethanol which is used in the Declaration for purposes of comparison is the same as the formulation of Example 3 of Padfield et al. Accordingly, the Declaration presents a direct comparison between a composition according to the present invention and a composition according to the prior art. . . . Applicant acknowledges that ethanol has previously been used in pharmaceutical compositions. However, the purpose for which ethanol has been included has been either as *a solvent or as a preservative against bacterial contamination*. There was, however, no reason to suppose that either of these functions of ethanol would have had any beneficial effects in terms of *limiting the degradation of ranitidine* in aqueous formulations thereof." (5/10/91 Request for Reconsideration, Ex. 3, G000205) (emphasis added).<br><br>**'249 prosecution history, Declaration of Dr. John Hempenstall executed April 12, 1991 (Ex. 3, G000208-11):**<br><br>"5. In my laboratory it was found that for an aqueous based ranitidine formulation, a significant and *surprising enhancement in the stability of ranitidine* is achieved by the addition of ethanol to the formulation.<br><br>* * *<br><br>6. . . . The acceptable shelf life for an aqueous formulation containing ranitidine hydrochloride is | |

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|---|---|---|
| | considered to be the time at which no more than 5% of the ranitidine present in the formulation has degraded. Accordingly, the figure determined from the stability studies was the time (in months) for 5% ranitidine loss calculated as the lower 95% confidence limit. The results are as follows: | |

| | Without Ethanol | | *With 7.5% Ethanol* | | |
|---|---|---|---|---|---|
| Temperature | Batch 1 | Batch 2 | Batch 3 | Batch 4 | Batch 5 |
| 30°C | 12.5 | 13.6 | 19.5 | 17.0 | 20.8 |
| 37°C | 5.4 | 4.7 | 7.8 | 7.1 | 7.5 |
| 45°C | 1.8 | 2.3 | 2.9 | 2.9 | 2.8 |

Thus, the formulation with ethanol has an average shelf life at 30°C of 19 months compared with 13 months when ethanol is excluded from the formulation. This is a highly significant and valuable improvement.

The stability of oral liquid formulations as described above except containing varying amounts of ethanol was also studied at 37°C and 45°C. The clear advantageous effects of the presence of ethanol can be seen from the following table which gives the time (in months) for 5% ranitidine loss (calculated as the lower 95% confidence limit).

| Claim Element | Glaxo's Position | Teva's Position |
|---|---|---|
| | Temperature / *% Ethanol*: 0 / *2.5* / *5.0* / *7.5* / *10.0*<br>37°C: 5.9 / 7.2 / 7.6 / 7.7 / 6.4<br>45°C: 2.1 / 2.4 / 2.4 / 2.6 / 2.7<br><br>7. The above results clearly show that ethanol has a beneficial effect upon the stability of ranitidine in aqueous based formulations and furthermore I am not aware of any teaching in the art that would lead me to expect such an effect." (5/10/91 Request for Reconsideration, Ex. 3, ¶¶ 5, 6, 7 at G000209-211) (emphasis added). | |
| Claims 3 (dependent on Claim 1) and 11<br><br>"7% to 8% weight/volume ethanol" | Glaxo's Proposed Construction: 7% to 8% weight/volume ethanol sufficient to enhance the stability of the ranitidine active ingredient in the aqueous formulation for oral administration.<br><br>Intrinsic Evidence:<br><br>**'249 patent, claim 1 (Ex. 1):**<br><br>"A pharmaceutical composition which is an aqueous formulation for oral administration of an effective amount of ranitidine and/or one or more | Teva's Proposed Construction: 7% to 8% weight/volume ethanol.<br><br>Intrinsic Evidence:<br><br>**'249 patent, claim 2 (Ex. 1):**<br><br>"2. A pharmaceutical composition according to claim 1 containing 2.5% to 10% weight/volume ethanol based on the complete formulation." |

| Claim Element | Glaxo's Position | Teva's Position |
|---|---|---|
| | physiological acceptable salts thereof, said formulation comprising *a stabilizing effective amount of* ethanol and said composition having a pH in the range of 6.5 to 7.5." (Emphasis added).<br><br>**'249 patent, claim 3 (Ex. 1):**<br><br>"A pharmaceutical composition according to claim 1 containing *7% to 8%* weight/volume ethanol based on the complete formulation." (Emphasis added).<br><br>**'249 patent, claim 11 (Ex. 1):**<br><br>"A pharmaceutical composition which is an aqueous formulation of ranitidine for oral administration containing 150 mg ranitidine per 10 ml dose expressed as a free base, said formulation having a pH in the range of 7.0 to 7.3 and also containing *7% to 8%* weight/volume ethanol based on the complete formulation." (Emphasis added).<br><br>Glaxo incorporates by reference all of the intrinsic evidence cited and quoted in the discussion of claims 1 and 2. In addition, Glaxo wishes to call the Court's attention to the following intrinsic evidence specifically related to claims 3 and 11.<br><br>**'249 patent, Col. 1:54-56 (Ex. 1):**<br><br>"The amount of ethanol present in the formulation is such that the resulting formulation has the *enhanced stability*. Preferably the amount of ethanol in the | **'249 patent, claim 3 (Ex. 1):**<br><br>"3. A pharmaceutical composition according to claim 1 containing 7% to 8% weight/volume ethanol based on the complete formulation."<br><br>**'249 patent, claim 11 (Ex. 1):**<br><br>11. A pharmaceutical composition which is an aqueous formulation of ranitidine suitable for oral administration containing 150 mg ranitidine per 10 ml dose expressed as free base, said formulation having a pH in the range 7.0 to 7.3 and also containing 7% to 8% weight/volume ethanol based on the complete formulation.<br><br>**'249 patent, claim 12 (Ex. 1):**<br><br>12. A pharmaceutical composition according to claim 11 wherein said pH is obtained by the use of buffer salts.<br><br>**'249 patent, Col. 2:30-34 (Ex. 1):**<br><br>"The amount of ethanol in the formulation for oral administration, expressed as a percentage of the complete formulation on a weight/volume basis, is preferably within the range 2.5 to 10%, and more particularly between 5 to 10%, more especially 7-8%." |

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| | evidence that the compositions of the present invention show a quite unexpected advantage over the teachings of GB-A-2142820 *in terms of the stability of the ranitidine in the composition*. In this connection, it is noted that the liquid formulation without ethanol which is used in the Declaration for purposes of comparison is the same as the formulation of Example 3 of Padfield et al. Accordingly, the Declaration presents a direct comparison between a composition according to the present invention and a composition according to the prior art. . . . Applicant acknowledges that ethanol has previously been used in pharmaceutical compositions. However, the purpose for which ethanol has been included has been either as *a solvent or as a preservative against bacterial contamination*. There was, however, no reason to suppose that either of these functions of ethanol would have had any beneficial effects in terms of *limiting the degradation of ranitidine* in aqueous formulations thereof." (5/10/91 Request for Reconsideration, Ex. 3, G000205) (emphasis added).<br><br>**'249 prosecution history, Declaration of Dr. John Hempenstall executed April 12, 1991 (Ex. 3, G000208-11):**<br><br>"5. In my laboratory it was found that for an aqueous based ranitidine formulation, a significant and *surprising enhancement in the stability of ranitidine* is achieved by the addition of ethanol to the formulation. | |

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| | * * *<br>6. . . . The acceptable shelf life for an aqueous formulation containing ranitidine hydrochloride is considered to be the time at which no more than 5% of the ranitidine present in the formulation has degraded. Accordingly, the figure determined from the stability studies was the time (in months) for 5% ranitidine loss calculated as the lower 95% confidence limit. The results are as follows: | |

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Thus, the formulation with ethanol has an average shelf life at 30°C of 19 months compared with 13 months when ethanol is excluded from the formulation. This is a highly significant and valuable improvement.

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<table>
<tr><td>Temperature</td><td colspan="5">% Ethanol</td></tr>
<tr><td></td><td>0</td><td>2.5</td><td>5.0</td><td>7.5</td><td>10.0</td></tr>
<tr><td>37°C</td><td>5.9</td><td>7.2</td><td>7.6</td><td>7.7</td><td>6.4</td></tr>
<tr><td>45°C</td><td>2.1</td><td>2.4</td><td>2.4</td><td>2.6</td><td>2.7</td></tr>
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<br>7. The above results clearly show that ethanol has a beneficial effect upon the stability of ranitidine in aqueous based formulations and furthermore I am not aware of any teaching in the art that would lead me to expect such an effect." (5/10/91 Request for Reconsideration, Ex. 3, ¶¶ 5, 6 and 7 at G000209-211) (emphasis added).</td><td></td></tr>
<tr><td>Claims 1-10<br><br>"aqueous formulation for oral administration"</td><td><u>Glaxo's Proposed Construction</u>: A water based formulation, wherein water is the solvent (i.e., the liquid present in the formulation in the largest amount), administered orally for gastrointestinal absorption.</td><td><u>Teva's Proposed Construction</u>: This clause need not and should not be construed, given Teva's judicial admission, as stated during the June 30, 2005 telephone conference with the Court.</td></tr>
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| | Intrinsic Evidence:<br><br>**'249 patent, Col. 1:40-44 (Ex. 1):**<br><br>"We have now surprisingly found that the stability of ranitidine in aqueous based formulations and more particularly *aqueous based formulations for oral administration* may be substantially enhanced by the addition of ethanol to the formulation." (Emphasis added).<br><br>**'249 patent, Col. 2:1-10 (Ex. 1):**<br><br>"A preferred embodiment of the invention is an *aqueous formulation for oral administration*. Such a formulation may comprise ranitidine and/or one or more of its physiologically acceptable salts *dissolved in water*, ethanol, a preservative and a viscosity enhancing agent. Preferably the required pH of the formulation is obtained by the use of appropriate buffer salts. Optionally the composition may also contain other conventional excipients such as a sweetener, a flavour and/or flavouring aids." (Emphasis added).<br><br>**'249 patent, Col. 2:38-43**<br><br>"The aqueous formulations for oral administration are conveniently prepared by mixing an aqueous solution of ranitidine and/or one or more of its physiologically acceptable salts together with ethanol and the excipients, with aqueous solution or | |

| Claim Element | Glaxo's Position | Teva's Position |
|---|---|---|
| | dispersion of the viscosity enhancing agent."<br><br>**'249 patent, Col. 2:47-65 (Ex. 1):**<br><br>"An illustrative example of a formulation according to the invention is as follows. . . .<br><br>Ranitidine oral liquid formulation (150 mg/10ml) expressed as free base<br><br>% w/v<br>Ranitidine hydrochloride 1.68<br>Ethanol 7.5<br>Potassium dihydrogen orthophosphate 0.095<br>Disodium hydrogen orthophosphate anhydrous 0.350<br>*Hydroxypropylmethylcellulose* *qs*<br>*Preservative* *qs*<br>*Sweetening agents* *qs*<br>*Flavour* *qs*<br>*Purified water BP to* *100ml.* "<br>(Emphasis added).<br><br>**'249 prosecution history, Declaration of Dr. John Hempenstall executed April 12, 1991 (Ex. 3, G000208-11):**<br><br>"5. In my laboratory it was found that for *an aqueous based ranitidine formulation*, a significant and surprising enhancement in the stability of ranitidine is achieved by the *addition of ethanol to* | |

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| | *the formulation.*<br><br>* * *<br><br>7. The above results clearly show that ethanol has a beneficial effect upon the stability of ranitidine in *aqueous based formulations* and furthermore I am not aware of any teaching in the art that would lead me to expect such an effect." (5/10/91 Request for Reconsideration, Ex. 3, ¶¶ 5 and 7 at G000209, 211) (emphasis added). | |
| Claims 11-12<br><br>"aqueous formulation of ranitidine suitable for oral administration" | Glaxo's Proposed Construction: A water based formulation of ranitidine, wherein water is the solvent (*i.e.*, the liquid present in the formulation in the largest amount), administered orally for gastrointestinal absorption.<br><br>Intrinsic Evidence:<br><br>**'249 patent, Col. 1:40-44 (Ex. 1):**<br><br>"We have now surprisingly found that the stability of ranitidine in aqueous based formulations and more particularly *aqueous based formulations for oral administration* may be substantially enhanced by the addition of ethanol to the formulation." (Emphasis | Teva's Proposed Construction: This clause need not and should not be construed, given Teva's judicial admission, as stated during the June 30, 2005 telephone conference with the Court. |

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| | **'249 patent, Col. 2:47-65 (Ex. 1):**<br><br>"An illustrative example of a formulation according to the invention is as follows. . . .<br><br>Ranitidine oral liquid formulation (150 mg/10ml) expressed as free base<br><br>% w/v<br>Ranitidine hydrochloride 1.68<br>Ethanol 7.5<br>Potassium dihydrogen orthophosphate 0.095<br>Disodium hydrogen orthophosphate anhydrous 0.350<br>*Hydroxypropylmethylcellulose* *qs*<br>*Preservative* *qs*<br>*Sweetening agents* *qs*<br>*Flavour* *qs*<br>*Purified water BP to* *100ml.* "<br>(Emphasis added).<br><br>**'249 prosecution history, Declaration of Dr. John Hempenstall executed April 12, 1991 (Ex. 3, G000208-11):**<br><br>"5. In my laboratory it was found that for *an aqueous based ranitidine formulation*, a significant and surprising enhancement in the stability of ranitidine is achieved by the *addition of ethanol to the formulation*. | |

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Dated: June 30, 2006

CONNOLLY BOVE LODGE & HUTZ LLP

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## CERTIFICATE OF SERVICE

I hereby certify that on June 30 2006, I electronically filed the foregoing **JOINT CLAIM CONSTRUCTION CHART FOR U.S. PATENT NO. 5,068,249** with the Clerk of Court using CM/ECF which will send notification of such filing and we will hand deliver such filing to the following:

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I hereby certify that on June 30, 2006, I have mailed via Federal Express, the document to the following non-registered participants:

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